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EXAMINER	
GODDARD, LAURA B	

ART UNIT	PAPER NUMBER
1642	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/525,011	NATUNEN ET AL.	
	Examiner	Art Unit	
	LAURA B. GODDARD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *87-147* is/are pending in the application.

4a) Of the above claim(s) *87-131 and 142-147* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *132-141* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed December 14, 2009 in response to the Office Action of June 12, 2009, is acknowledged and has been entered. Claims 87-147 are pending. Claims 137 and 138 are amended, although the status identifier of claim 137 does not indicate this. Claims 140-147 are new. Claims 87-131 remain withdrawn.

2. Claims 142-147 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions for the reasons set forth below.

3. The inventions as listed do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the reasons previously set forth in the restriction mailed January 14, 2008. Claims 142 and 144 as currently constituted are directed to the special technical feature of a cell or tissue that is covalently modified by the composition or claim 132 or 143, hence the invention of claims 142 and 144 do not comprise the special technical feature of Group X as originally presented in application, that is a composition comprising an enzyme substrate that is a 2-modified monosaccharide reside or a modified monosaccharide residue. Claims 143 and 145-147 as currently constituted are directed to the special technical feature of a composition comprising an enzyme substrate and a transferring enzyme, hence claims 143 and 145-147 are drawn to a s composition comprising a different special technical feature from Group X as

originally presented in application, that is a composition comprising an enzyme substrate that is a 2-modified monosaccharide reside or a modified monosaccharide residue, and is not required to have a transferring enzyme.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 142-147 are withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R. 1.142(b) and MPEP 821.03.

4. Claims 132-141 are currently being examined, wherein claims 140 and 141 are new.

Maintained Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. **Claims 132-135 remain rejected** under 35 U.S.C. 102(b) as being anticipated by Bulter et al (Chemobiochem, 2001, 2:884-894) (see section 6 of the previous Office Action).

Bulter et al teach a composition comprising an enzyme substrate, UDP-6-biotinyl-Gal or UDP-6-biotinyl-GalNAc, that is capable of being transferred by galactosyltransferase (a glycosyl transferase) to acceptor structures such as BSA-$(GlcNAc)_{17}$ and ovalbumin, and is a carbohydrate substance (abstract, p. 885; Scheme 1 and 2; Figures 3-7). Bulter et al teach the selective transfer of labeled nucleotide sugars onto specific acceptor structures in a glycoplipid or glycoprotein by glycosyltransferases, and teach that certain acceptor structures have tissue and cell-type specific expression associated with diseases such as cancer (p. 884, col. 1; p. 885, col. 1; p. 890, col. 1, paragraph 2; col. 2, last paragraph). Bulter et al teach the production of nonradioactive-labeled (fluorescein) or tagged (biotin) UDP-Gal and UDP-GalNAc for diagnostic applications (p. 885, col. 1). Biotin can elicit an immune response, hence would be an immunologically active substance.

Response to Arguments

6. Applicants argue that the invention is distinct from Bulter because Bulter describes 6-modified monosaccharides, not 2-modified monosaccharide residues (p. 24-25).

This argument is partially persuasive and the claims limited to 2-modified monosaccharide residues have been withdrawn from rejection. However, the arguments are not persuasive for the claims drawn broadly to an enzyme substrate that is a modified monosaccharide reside. Applicants admit on the record that Bulter describes a 6-modified monosaccharide, therefore Applicants acknowledge that Bulter anticipates the broadly claimed substrate that is a modified monosaccharide residue (see page 14, first paragraph, previous Office Action).

7. **Claims 132-139 remain rejected under 35 U.S.C. 102(e)** as being anticipated by US patent 7,265,084, DeFrees et al, filed April 9, 2003, issued September 4, 2007 (see section 4 of the previous Office Action).

DeFrees et al teach the enzyme substrates UDP-galactose, UDP-glucose, UDP-mannose, UDP-galactosamine, and UDP-glucosamine, wherein the monosaccharide (galactose, glucose, mannose, galactosamine, or glucosamine) of the substrates has a 2-position modified by the addition of groups including: O, NH, S, CH_2, a linker, and a ligand of interest including: PEG, VEGF, FGF, protein, chondroiton, keratan, integrins, and peptides (col. 11, lines 30-50; col. 172-col. 174, table 4). These substrates would encompass the formula UDP-GalN[-S-]-D or UDP-GalN-D as instantly claimed. DeFrees et al teach the peptides or proteins linked to the substrates can be therapeutic agents or agents for diagnosis including toxins, prodrugs, and radioisotopes (col. 45, lines 21-67; col. 143, line 44 to col. 42).

Response to Arguments

8. Applicants argue that the invention of DeFrees appears not to have been brought to practice with regard to the 2-modified monosaccharide residue (or other monosaccharide derivatives except specific sialic acid derivatives). Applicants point to Bulter for evidence and argue that the synthesis of modified nucleotide sugars is not trivial and may fail unexpectedly. Applicants argue that Bulter managed to produce its molecule effectively after several serious problems in many steps, such as inactivation of the galactose oxidase enzyme and needing to include unusual step by frozen solid phase synthesis in -20°C temperatures (p. 27).

The arguments have been considered but are not found persuasive. The claims are drawn broadly to 2-modified monosaccharide residues and modified monosaccharide residues as enzyme substrates. As stated above by Examiner, Bulter provides evidence that making modified monosaccharide residues is known and enabled. The evidence that Applicants point to for difficulties in making the modified monosaccharide are not sufficient evidence to demonstrate that the process of making modified or 2-modified monosaccharide residues was unknown or not possible at the time of the DeFrees invention. For example, the inactivation of galactose oxidase enzyme in Bulter (p. 887, lines 4-6) was only a problem of optimizing *large scale production* of the modified monosaccharide, not a problem in the process of making the molecule itself. The problem of an "unusual" step of frozen solid phase synthesis in Bulter was actually part of a step of optimizing molecule synthesis in a wide range of temperatures, from -80 to 37 °C (Figure 2). Bulter not only teaches methods of

optimizing modified monosaccharide synthesis, Bulter demonstrates such methods of making modified monosaccharides were known and successful. MPEP 2121.02 states: a reference is presumed operable until applicant provides facts rebutting the presumption of operability. In re Sasse, 629 F.2d 675, 207 USPQ 107 CCPA 1980). Therefore, applicant must provide evidence showing that a process for making was not known at the time of the invention. The fact that an author of a publication did not attempt to make the compound disclosed, without more, will not overcome a rejection based on that publication. In re Donohue, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985). The modified or 2-modified monosaccharide residues taught by DeFrees are presumed operable and Applicants have not successfully shown that the process for making the modified or 2-modified monosaccharide residues was not known at the time of the invention.

9. Applicants argue that present invention revealed 2-modified monosaccharides with reactive linking group and this is claimed in new claim 140 (p. 27).

Examiner did not reject claim 140 as being anticipated by DeFrees.

10. Applicants argue that there is no evidence of reactions to cells or tissues in DeFrees. Applicants argue that specific enzymes are needed to transfer the modified monosaccharide and alteration of donor structure may affect the accept specificity (p. 28).

The arguments have been considered but are not found persuasive because Applicants are arguing limitations not recited in the claims. There is no specific enzyme requirement recited that would exclude the substrates taught by DeFrees and Applicants have not shown how the structure of the claimed enzyme substrates are different from the substrates taught by DeFrees.

11. Applicants argue that DeFrees does not provide experimental evidence of an enzyme effectively transferring 2-modified galactose/galactosamine and the embodiment was not brought into practice. Applicants argue screening is needed to find molecules that would work with the transferases based on the broad description of DeFrees (p. 28).

The arguments have been considered but are not found persuasive for the reasons set forth above in sections 8 and 10. Further, Applicants have not shown how the enzyme substrates of DeFrees are different from the claimed substrates.

New Rejection

(based on new considerations)

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 132-141 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a WRITTEN DESCRIPTION rejection.

The claims broadly encompass any 2-modified monosaccharide residue or modified monosaccharide residue enzyme substrate that has the function of being transferred specifically to a surface of a pathogenic entity or malignant cell or tissue by a transferring enzyme making a covalent linkage between said enzyme substrate and an acceptor structure of said surface for use as a medicine; any glycosyltransferase, transglycosylating enzyme, transglycosylating enzyme, transsialidase, engineered galactosyltransferase from animals or any natural GalNAc/GlcNAc-transferase with any similarity to the engineered galactosyltransferase, wherein the enzymes have the function of transferring the substrate to a surface of a pathogenic entity or malignant cell or tissue by making a covalent linkage between the enzyme substrate and an acceptor structure of said surface for use as a medicine; wherein the substrate is any carbohydrate substance that has the function of being transferred specifically to the surface of a pathogenic entity or malignant cell or tissue by the transferring enzyme, wherein the substrate is any modified monosaccharide or 2-modified monosaccharide with the formula USP-GalN[-S-]-D.

The specification only discloses enzyme substrates 2-modified galactosamine with the formula UDP-GalN[-S-]-D, that can be transferred by the animal enzyme β1,4-

Galactosyltransferase I (β4Gal-T1), wherein the enzyme has a specific mutation that allows transfer of modified monosaccharides. The specification discloses that an enzyme was used based on the enzyme produced by Ramakrishnan and Qasba (J of Biological Chemistry, March 2002, 277:20833-20839). Ramakrishnan and Qasba teach this specific enzyme as bovine β4Gal-T1 with a mutation of tyrosine-289 to Leu, Ile, or Asn that enhances the enzyme activity, wherein Y289L exhibited Gal-NAc-transferase activity that was nearly 100% of its Gal-T activity (abstract). The specification discloses that human β4Gal-T1 can be used with the same mutation and such an enzyme is capable of transferring of a monosaccharide unit modified to position 2 ([0155-0156]). The specification discloses that the enzyme catalyzed the *ex vivo* transfer of GalN-PEG-fluorescein groups from UDP-GalN-PEG-fluorescein to non-reducing terminal N-acetylglucosamine (GlcNAc) residues present in glycoprotein glycans of human tumor cells and tumor tissue sections (Example 13). The specification discloses the incorporation of carboxiilic acid reagents into the 2-amino group of uridine diphosphogalactosamine, which are suitable for protein-compatible water-solution coupling of N-maleimido, aldehyde, and thiol group containing reagents or biologically active substances. The reagents were incubated in aqueous solution with a non-reducing terminal N-acetylglucosamine containing glycoconjugate and a modified galactosyltransferase enzyme similar to the one described by Ramakrishnan and Qasba (above), which resulted in the successful transfer of conjugation reagent-modified galactosamine residues to the glycoconjugates ([0276], Example 14). The specification discloses making UDP-GalN-biotin (Example 4). Labeling of terminal GlcNAc residues

in oligosaccharides and tissue sections with UDP-GalN-biotin. N-(6-biotinamidohexanoyl) galactosamine can be transferred from UDP-GalN-biotin to a terminal GlcNAc containing acceptor with a recombinant β1,4-galactosyltransferase similar to the enzyme described in Ramakrishnan and Qasba (above). The specification does not disclose any other modified monosaccharides or any 2-modified monosaccharides other than 2-modified galactosamine with the formula UDP-GalN[-S-]-D that can be capable of being transferred to a surface of a cancer cell or tissue as claimed; and the specification does not disclose any other glycosyltransferases, transglycosylating, transsialidase, or engineered galactosyltransferase enzymes, other than bovine or human β4Gal-T1 with mutation Y289L, that would function as broadly claimed.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a recitation of "modified monosaccharide residue," "2-modified monosaccharide residue," "capable of being transferred specifically to a surface of a pathogenic entity or malignant cell or tissue by a transferring enzyme making a covalent linkage between said enzyme substrate and an acceptor structure of said surface for use as a medicine," wherein the enzyme is a "glycosyltransferase," "transglycosylating enzyme," "transsialidase,"

"engineered galactosyltransferase from animals," or "natural GalNAc/GlcNAc-transferase with similar specificity with said engineered galactosyltransferase." Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that " [a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name', of the claimed subject matter sufficient to distinguish it from other materials. " Id. At 1567, 43 USPQ2d at 1405. The court also stated that:

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. Thus, the instant specification may provide an adequate written description of modified monosaccharide residue and 2-modified monosaccharide residue substrates, and

glycosyltransferase, transglycosylating enzyme, transsialidase, engineered galactosyltransferase from animals, and natural GalNAc/GlcNAc-transferase with similar specificity with said engineered galactosyltransferase that all function to transfer the broadly claimed substrate specifically to a surface of a pathogenic entity or malignant cell or tissue by making a covalent linkage between said enzyme substrate and an acceptor structure of said surface for use as a medicine, per Lilly by structurally describing representative monosaccharide residue and 2-modified monosaccharide residue substrates and enzymes or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not directly describe the modified monosaccharide residue, 2-modified monosaccharide residue substrates, and enzymes useful in the claimed invention in a manner that satisfies either the Lilly or Enzo standards. Although the specification discloses enzyme substrates 2-modified galactosamine with the formula UDP-GalN[-S-]-D that can be transferred by the human or bovine enzyme β1,4-Galactosyltransferase I (β4Gal-T1) with a specific mutation Y289L that allows transfer of modified monosaccharides, this does not provide a description of the broadly claimed modified monosaccharide residue, 2-modified monosaccharide residue substrates, and enzymes that function as claimed that would

satisfy the standard set out in Enzo because the specification provides no structural features coupled to the functional characteristics.

Further, the specification also fails to describe the modified monosaccharide residues, 2-modified monosaccharide residue substrates, and enzymes that function as claimed by the test set out in Lilly because the specification describes only enzyme substrates 2-modified galactosamine with the formula UDP-GalN[-S-]-D that can be transferred by the human or bovine enzyme β1,4-Galactosyltransferase I (β4Gal-T1) with a specific mutation Y289L that allows transfer of modified monosaccharides. Therefore it necessarily fails to describe a representative number of such species.

Thus, the specification does not provide an adequate written description of the modified monosaccharide residue, 2-modified monosaccharide residue substrates, and enzymes that function as claimed that is required to practice the claimed invention.

13. All other rejections recited in the Office Action mailed June 12, 2009 are hereby withdrawn in view of amendments and arguments.

14. **Conclusion:** No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA B. GODDARD whose telephone number is (571)272-8788. The examiner can normally be reached on 7:00am-3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Laura B Goddard/
Primary Examiner, Art Unit 1642